DIP #595

Step 2/3 Rapid Review Series (121)

Disclaimer:

This transcript is a written adaptation of the original audio content produced by *Divine Intervention Podcasts*. All credit for the intellectual content, teaching points, and clinical insights belongs solely to Dr. Divine and the Divine Intervention platform.

This transcription has been created **for educational purposes only** to assist fellow students in their USMLE preparation. I do **not charge anything** for this and have no commercial intent—this is purely a free, volunteer effort to make the material more accessible in text format.

I do **not claim ownership** of the original material. If you find this helpful, I strongly encourage you to support the original creator by visiting www.divineinterventionpodcasts.com and listening to the content directly.

- **Dr Mohammed Zaki**
https://chat.whatsapp.com/L6dShASc3f97cwHZgCD6Xo

Welcome. My name is Divine. This is Episode 595 of the Divine Intervention Podcasts. In today's podcast, we're going to be continuing the Rapid Review series for the USMLE Step 2 CK and Step 3 exams. This is going to be Series 121. And again, I just want to send a quick note to those of you studying for Step 2 and Step 3. I would strongly encourage you, if you can, to take the Step 1 Free 120. Just add it to the list of practice exams you're taking, and then please listen to the series I have on it.

CONGENITAL HEART DISEASE ASSOCIATIONS

So, first things first—what if they give you a question about a lady, and they tell you that she has a history of bipolar disorder and that she delivers a newborn? And this newborn has signs and symptoms of heart failure. You're told that she was diagnosed with bipolar disorder two years ago and was started on pharmacotherapy. Let me ask you this: What should be your diagnosis here? What's the cause of the heart failure symptoms in her child?

I would really hope you're thinking about Ebstein's anomaly. So this child has Ebstein's anomaly. Remember, in Ebstein's anomaly, we typically see it in association with lithium. So mom has bipolar disorder. Lithium is a very good mood stabilizer. The thing is, one problem lithium can cause—although it's not very common—but it certainly is associated with lithium use, is that lithium can cause downward displacement of the tricuspid valve leaflets. In addition to that, the right ventricle does not develop as well as it should. So they can have a lot of issues with tricuspid regurgitation and things like that. Those are very common things we see in Ebstein's anomaly.

Sometimes, our friends at the USMLE will ask you, "Which of the following additional cardiac abnormalities will be found on further evaluation of this patient?" You want to pick the answer that talks about an atrial septal defect or a patent foramen ovale. This is very, very high yield to know for the USMLE exams. ASDs and PFOs have a very strong association—very, very strong association—with Ebstein's anomaly.

OK, so again, whenever there is a disorder and it has a congenital cardiac association, that's usually pretty high yield to know for purposes of your exams. ASDs and PFOs have a strong association. In fact, about half of the kids that have Ebstein's anomaly will have an ASD or a PFO. Please make sure that for your exams.

Let's think of some other disorders—like DiGeorge syndrome—where your third and your fourth pharyngeal pouches do not form. So you have no thymus, you have no parathyroid glands. What cardiac issues are associated? Don't forget truncus arteriosus and tetralogy of Fallot. They are very strong associations with DiGeorge syndrome.

How about Down syndrome? What's the strong cardiac association with Down syndrome? The strong cardiac association with Down syndrome is an endocardial cushion defect—sometimes called an atrioventricular canal defect.

How about fetal alcohol syndrome? What's the cardiac association to know? Fetal alcohol syndrome is associated with VSD—ventricular septal defects. VSDs have a very, very strong association with fetal alcohol syndrome.

How about Marfan syndrome? Remember, Marfan syndrome has a very strong association with mitral valve prolapse. Marfan's is an autosomal dominant disorder—chromosome 15, fibrillin gene defect. It has a very strong association with mitral valve prolapse, and it also has a very strong association with aneurysms of the aorta. So if you see sudden-onset severe chest pain in a person who is very tall on your exams—besides thinking of a pneumothorax, because that may be found in tall, thin young males—also think of Marfan's. Think of Marfan's with aortic dissection or the rupture of an aortic aneurysm.

Many of you are used to aortic dissections with Marfan's, but I kid you not—they can absolutely, positively just give you a thoracic aortic rupture question for a person that has Marfan's, and they may not give you dissection. OK, so please keep that at the back of your mind as you prepare for your test.

And remember, those people need immediate surgery. If not, the risk of death is extremely high. In fact, this is one of the reasons why people that have Marfan's get fairly regular screening echocardiograms—just to look at their hearts and also to look at the aortic wall.

Also, don't forget another disorder that is associated with mitral valve prolapse: autosomal dominant polycystic kidney disease, ADPKD. Remember, people that have ADPKD have a cluster of problems. They're going to have cysts in the liver—so they can get signs and symptoms of liver failure. They can have cysts in the kidneys. And remember, some of those cysts, unfortunately, can transform and become renal cell carcinoma. But they can also have mitral valve prolapse. They can also have aneurysms in the circle of Willis, and those aneurysms can rupture and cause a brain bleed. The person can have a brain bleed. So please make sure you know that stuff for your exams.

SMOKING-RELATED POLYCYTHEMIA

Now, what if they give you a question about a 57-year-old male, and they tell you that he has smoked two packs of cigarettes daily for the past 30 years? And then we're told that this man has a ruddy appearance to his skin, and you're told that his hematocrit is 63%. Obviously, this person has really bad polycythemia. Then they ask you: what is the mechanism behind this person's polycythemia?

I would really hope you're saying, "Oh, Divine, this person has polycythemia because of hypoxemia-induced erythropoietin secretion." Remember, when a person has COPD—for example, emphysema, which is probably the most common one that is tested on exams—you have a lot of proteases that are destroying your lung parenchyma. As those proteases destroy your lung parenchyma, you are losing surface area, and when you have surface area loss, you will have issues with diffusion.

Remember, the diffusibility of a gas is directly related to the surface area available and inversely related to the thickness of the wall separating the gases. So in the case of COPD, the mechanism behind the hypoxemia is a decrease in the surface area available for diffusion. Because the surface area for diffusion has decreased, you don't have proper equilibration of oxygen between the lumen of the alveoli and your pulmonary vessels. So that person develops hypoxia.

Whenever hypoxia develops, remember—that will cause the kidneys to produce erythropoietin. And that erythropoietin can cause polycythemia.

We can see the exact same problem in a patient that has cystic fibrosis. These people cannot clear their respiratory secretions very well. So, since they can't clear their respiratory secretions very well, over time they can develop pulmonary hypertension, they can develop pulmonary problems, and they can have a lot of hypoxia. That hypoxia can lead to the development of polycythemia from increased erythropoietin production.

Now, what is one very clever thing that our friends at the NBME can do to mess you up with polycythemia in a smoker? This is where you have to be abundantly cautious and careful on your exams. Polycythemia in a smoker on the USMLE is probably going to be caused by hypoxemia from chronic obstructive pulmonary disease. But one other thing in a smoker that can cause polycythemia is renal cell carcinoma.

"Divine, how? Where is that relationship coming from?"

Well, let me ask you this—what is the biggest risk factor for renal cell carcinoma? The biggest risk factor for renal cell carcinoma is smoking. So what's the link between renal cell carcinoma and polycythemia? The link is that renal cell carcinoma can produce EPO in a paraneoplastic fashion. It can produce erythropoietin in a paraneoplastic fashion, and that can absolutely, positively cause polycythemia.

So what are some other causes of polycythemia on the exams, especially from a malignancy perspective? Don't forget hepatocellular carcinoma. HCC can make EPO in a paraneoplastic fashion. Don't forget hemangioblastoma. Hemangioblastomas—remember, those have a very strong association with von Hippel-Lindau disease. And the key associations to know there—if a person has hemangioblastomas—it's going to show up as a posterior fossa mass, it's going to have calcifications, it's going to have like a mural nodule. Basically, it's going to have an intraluminal calcification. Those things can make EPO in a paraneoplastic fashion.

In fact, what is another unusual cause of polycythemia that you may see on your exams? Think of a cyanotic congenital heart defect. That is one backhanded way our friends at the NBME can test cyanotic congenital heart defects. So things like tetralogy of Fallot, or things like truncus arteriosus, or transposition of the great vessels, or total anomalous pulmonary venous return. All those are cyanotic congenital heart defects. That cyanosis can trigger the production of EPO. And that EPO that is produced can cause polycythemia.

So please make sure you can make all these integrations as you prepare for your exams.

And I guess, since I'm kind of talking about this—so what is the most common cause of polycythemia? Let me ask you this: What is the most common cause of polycythemia in general? The most common cause of polycythemia is hypoxemia caused by pulmonary disease. I'm going to say that again: The most common cause of polycythemia in general is hypoxemia caused by pulmonary disease.

POLYCYTHEMIA VERA (PV):

And I guess since we're talking about this polycythemia business, let's talk about a few more things that are related to polycythemia. Because again, many of you are probably familiar with polycythemia vera. We know that polycythemia vera is one of these myeloproliferative disorders from a JAK2 mutation. So your red blood cell precursors proliferate in an EPO-independent fashion.

In fact, let me tell you this—our friends on the NBME, sometimes instead of writing "polycythemia vera" as an answer, they will write "EPO-independent red blood cell proliferation" as the answer instead of PV.

But the thing that's going to happen is the USMLE employs that same strategy. They know that many people have Anki decks, pathologies. So what do they do? These days on exams, they take it, and they address it in a somewhat different way. So remember, another name you may see for polycythemia vera on your exams is "EPO-independent red blood cell proliferation."

PV: COMPLICATIONS

Because again, if you notice, I've given so many examples of how polycythemia may arise—those were examples of polycythemia from elevated EPO. But polycythemia vera is a cause of polycythemia that is not associated with an elevation in EPO. If anything, it is associated with a decrease in EPO. So the thing that is causing your red blood cells to proliferate like crazy is not EPO—it's the JAK2 mutation. It's an EPO-independent red blood cell proliferation.

And again, remember, people that have polycythemia vera—they can have a bunch of problems. They can have a lot of thrombosis. You may wonder, "Divine, why do they have a lot of thrombosis?" They have a lot of thrombosis because they have increased blood viscosity.

Because remember, these people have polycythemia, so their hematocrit is elevated. If your hematocrit is elevated, that is going to cause blood stasis. There is a very big difference between the way that water flows and the way that grease flows. I'm going to say that again: there is a big difference between the way water flows and the way grease flows. Water is a less viscous fluid, so it can flow very easily. But grease is a more viscous fluid, so it doesn't flow as easily. If something doesn't flow easily, that thing has stasis.

And if you remember Virchow's triad of hypercoagulability—remember the mnemonic for it is "SHE." S for stasis, H for hypercoagulability, and E for endothelial dysfunction. That blood stasis arises in polycythemia vera because they have increased blood viscosity. So because their blood is static, the clotting factors have more time to hang out together. Think about it—whenever things slow down, more interactions can happen. More interactions can happen between your clotting factors. If that happens, then you're going to have a lot of thrombosis.

You can have things like, for example, hepatic vein thrombosis—Budd-Chiari syndrome. This is why Budd-Chiari syndrome is quite common in polycythemia vera, because of that blood stasis leading to hypercoagulability. Again, do not forget Virchow's triad.

Also, these people can even have high blood pressure. The high blood pressure makes a lot of sense. Why does it arise? Their blood is very viscous because they have polycythemia. When your blood is viscous, that actually raises your total peripheral resistance. That raises your total peripheral resistance.

Why did I establish this relationship? It all goes back to our fancy principle you probably remember learning when you were studying for Step 1—and that's known as Poiseuille's Law. In Poiseuille's Law, remember, viscosity is directly related to total peripheral resistance. What is Poiseuille's Law? Basically, the radius of the vessel is inversely related to total peripheral resistance—to the fourth power—and then viscosity is directly related to total peripheral resistance. The length of the vessel is also directly related to total peripheral resistance.

So because these people have very viscous blood, their total peripheral resistance increases. And if total peripheral resistance increases, that's going to cause you to have hypertension. In fact, they can give you a question about an S4 heart sound in a person who has polycythemia vera. Or they can give you a question about a person that died from polycythemia vera, and then they provide a pathological image on your exams that shows concentric hypertrophy. Then they can ask you, "What is the mechanism behind the findings seen on autopsy evaluation of this patient?" Pick the answer that says "increased left ventricular afterload."

Again, what is the link? Remember—hypertension increases afterload. You may wonder, why? The thing is, if your blood pressure is very, very high, it's going to make it so that your left ventricle has to generate a lot of pressure to overcome the pressure in your aorta to push blood out. Because remember, flow happens from high pressure to low pressure. If you want blood to come out of your heart and to perfuse your systemic vessels, the pressure within the left ventricle—the systolic pressure within the left ventricle—has to be more than the systolic pressure that exists in your peripheral vessels.

So if you have a high blood pressure reading—let's say your BP is like 180/120—then your left ventricle has to generate systolic pressures higher than 180 mmHg to push blood out. If that happens, that pressure overload—that chronic pressure overload—on the left ventricle will lead to the development of concentric hypertrophy. That's because you're laying down sarcomeres in parallel. That will ultimately cause diastolic dysfunction of the heart. That will cause heart failure with preserved ejection fraction. Although many times, those people will have a decreased ejection fraction, it will not be as profoundly decreased as the person who has systolic heart failure—but it will be decreased nonetheless.

They will have that diastolic heart failure. They will have issues with ventricular filling. The left ventricular wall will be very thick, big, and beefy. And as you have blood striking the walls of that big, beefy left ventricle, that is going to cause you to have that S4 heart sound. That S4 heart sound.

Again, please—these integrations I'm talking about—you may be like, "Well Divine, you're going ham on basic sciences today." I promise you, this stuff may sound like basic sciences, but it sounds an awful lot like the things that pop up on the USMLE Step 2 and Step 3 exams these days. Do not sleep on these things I'm discussing. Make sure you understand these mechanisms. And that's why I'm trying to be very systematic, and I'm trying to be very slow in going through these things. I'm trying to be very methodical in going through these things. I promise you—it's going to be for your best benefit on your exams. It's going to be for your best benefit on your exams.

In fact, let's make some more integrations. Let's use polycythemia vera—I love Vera—because there are so many different topics you can touch on with Vera. So many different topics you can touch on with PV.

So for example, they can ask: People that have PV tend to have a lot of bleeding. What's the mechanism behind the bleeding in a person that has polycythemia vera? Well, the reason behind that is that they have an acquired von Willebrand factor deficiency.

"Divine, what? Acquired von Willebrand factor deficiency? What do you mean?"

Well again, let's go back to what we've discussed. We've said that people who have polycythemia vera have a very high risk of thrombosis. When you have increased thrombosis, that's going to cause a consumptive coagulopathy. That's going to cause a consumptive coagulopathy. Because think about it—what are the raw materials that are necessary for the formation of a thrombus? The raw materials are things like von Willebrand factor, things like GP1b, things like GP2b/3a.

So these people—it's a chronic problem they have. It's not like the polycythemia vera just self-resolves—no, it does not self-resolve. So because they are always in thrombosis land, thrombosis land—let me explain the mechanism—because of the increased blood viscosity, because they're always in thrombosis land, they keep using up their von Willebrand factor, keep using up their von Willebrand factor, keep using up their von Willebrand factor. So that causes them to develop an acquired von Willebrand factor deficiency.

So they may be forming a lot of thrombi, but they may also be bleeding. Please make sure you know that for your exams.

Now, remember—what if you see a person that has polycythemia vera and the person has enlargement of their left upper quadrant? That's a part of splenomegaly. It's because they have a lot of vascular congestion. That's going to be the mechanism behind that. Because again, remember, these people have crazy high hematocrits.

Or what if they give you a question about sudden-onset severe joint pain that developed very acutely in a person that has polycythemia vera? You want to think about gout.

What is the mechanism behind that gout? Well, remember—whenever a lot of cells are being broken down, they can release nucleic acid material into the circulation. Especially purines—they can ultimately be converted to uric acid. That hyperuricemia can lead to the development of gout.

So these people can absolutely have gout. Because think about it—they have a lot of red blood cells. All these red blood cells are breaking down. And because these red blood cells are breaking down, you're releasing a lot of cell contents into the bloodstream. That material can be converted by xanthine oxidase into uric acid. And these people can have hyperuricemia, and they can have gout as a problem.

Again, you never thought you could get all these things from polycythemia vera. You absolutely can.

In fact, when you see the USMLE talk about this nebulous part of the exam called "multi-system processes and disorders," this is precisely what they are talking about. I'm going to say that again—when you hear our friends at the NBME talking about multi-system processes and disorders, they're literally talking about something like this, where you can take one topic and create so many different integrations from it. Like literally, there are like 20 exam questions you can write—full-fledged multiple-choice, long-stem questions—just from polycythemia vera.

PV: TREATMENT

And don't forget—how do we treat polycythemia vera? You've got to do phlebotomy. We've got to reduce hematocrit. Because if you notice, this increased blood viscosity—this polycythemia—is causing so many of their problems. So let's bleed these people—in a controlled fashion, do some phlebotomy. And in addition to that, also give them aspirin. You're basically taking advantage of its antithrombotic properties. Its antithrombotic properties.

Because remember, aspirin is an irreversible inhibitor of COX-1 and COX-2. By doing that, it's going to reduce the synthesis of thromboxane A2. When you reduce the synthesis of thromboxane A2, you are going to help in shutting down platelet aggregation. So that's going to be very helpful.